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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/565,885	01/25/2006	Juan Lopez De Silanes	2399.0080000/JAG/PAJ	8053

26111 7590 07/31/2009
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EXAMINER	
SKELDING, ZACHARY S	
ART UNIT	PAPER NUMBER
1644	
MAIL DATE	DELIVERY MODE
07/31/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/565,885	LOPEZ DE SILANES ET AL.	
	Examiner	Art Unit	
	ZACHARY SKELDING	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62-65* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62-65* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7-6-09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks filed February 17, 2009 are acknowledged.

   Claims 1-61 have been canceled.

   Claims 62-65 have been added.

   Claims 62-65 are under examination wherein the elected species of disorder is "corneal transplant rejection".

2. This Office Action is in response to Applicant's amendment and remarks filed February 17, 2009.

   The previous rejections of record can be found in the Office Action mailed September 15, 2008.

   The previous objections to the specification and claims have been withdrawn in view of applicant's amendment to the claims.

   The previous rejections under 35 U.S.C. 103(a) has been withdrawn in view of applicant's amendment to the claims.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

   (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. New claims 62, 64 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over John Pluenneke (US 2001/0021380) in view of Fabrizio et al. (EP 0 492 448 A1), Horwitz (WO 92/22324, cited on an IDS), Adair et al. (EP 0 516 785 B1) and Reza Dana (WO 00/27421), essentially for the reasons of record as put forth in the prior Office Action mailed September 15, 2008 and as further described below.

   While this is a new grounds of rejection as applicant has canceled all of the previously pending claims and added new claims 62, 64 and 65, the reference teachings put forth in the previous Office Action - Pluenneke in view of Fabrizio, Horwitz, Adair and Reza Dana - are as applicable to the instant claims as they were to the previously pending claims. Thus, the instant rejection is put forth in response to applicant's patentability arguments as described further below.

Applicant's arguments

Applicant argues a prima facie case has not been established for the claimed invention because there was allegedly no motivation for one of ordinary skill in the art to use an F(ab')2 anti-TNFa fragment to treat corneal transplant rejection and because one of ordinary skill in the art would allegedly not have had a reasonable expectation of success in doing so.

Applicant's arguments have been considered, but have not been found convincing, essentially for the reasons of record as put forth in the Office Action mailed September 15, 2008.

Motivation to combine

Applicant argues the claimed invention is non-obvious because "none of the cited references discloses the capability of F(ab')2 anti-TNFa fragments to penetrate the cornea or the level of immunogenicity of F(ab')2 anti-TNFa fragments in treating corneal transplant rejection." Thus, applicant concludes "at best, the combination of the prior art references are invitation to experiment." (see remarks page 7, 1st paragraph to page 8, 1st paragraph).

With respect to the penetration aspect of F(ab')2 anti-TNFa fragments, at page 7, 1st paragraph of the Remarks applicant describes in detail the structure of the cornea and concludes "[i]n light of these special features, Applicants submit that it was not predictable, at the time the instant invention was made, that the F(ab')2 antibody fragments would better penetrate the cornea even if the fragments might better penetrate a tumor tissue."

Applicant's argument is not found convincing because applicant has not provided sound scientific reasoning or objective evidence *why* one of ordinary skill in the art would have considered the ability of an $F(ab')_2$ antibody to penetrate the cornea any different than the ability of an $F(ab')_2$ antibody to penetrate any other tissue, e.g., tumor tissue.

Furthermore, as put forth in the previous Office Action at page 5, 4th paragraph, "One of ordinary skill in the art would have had a reasonable expectation of success in treating corneal allograft rejection via topical administration of a TNFα antagonist, such as an anti-TNF $F(ab')_2$, not only in view of the teachings of Pluenneke but also given the successful treatment of murine corneal allograft rejection via topical administration of a different TNFα antagonist, soluble TNF receptor I (see Reza Dana, in particular, Figures 3 and 6; page 9, 1st paragraph; the paragraph bridging pages 12-13)."

In other words, given the small size of $F(ab')_2$ antibodies, their lack of an FcR binding site and their consequent tissue penetrating abilities as taught by Horwitz (see, e.g., paragraph bridging pages 14-15), why would one of ordinary skill in the art consider corneal penetration unpredictable, especially so when a larger TNFα antagonist that binds FcR, such as the TNFR-Fc antagonist exemplified by Reza Dana (@150 kDa vs. @100 kDa), is capable of treating corneal transplant rejection in a mouse model?

With respect to "the level of immunogenicity of F(ab')2 anti-TNFa fragments" applicant argues "[a]lso unlike other types of tissues, the cornea has low constitutive expression of major histocompatibility complex (MHC) antigen, and it does not have centrally situated

antigen-presenting cells. *Id.* However, in the cornea, there is local production of immunosuppressive cytokines and expression of Fas ligand. *Id.* These features alter both the induction and expression of alloimmunity. *Id.* Because of these special immune-reaction-related features in the cornea, it was not predictable, at the time of the instant invention was made, that the lower level of immunogenicity of F(ab')2 antibody fragments would occur in treating corneal transplant rejection." (see Remarks paragraph bridging pages 7-8).

Applicant appears to be implying by their argument that somehow F(ab')2 antibody fragments could not be predicated by one of ordinary skill in the art to have a lower level of immunogenicity compared to larger anti-TNFα antagonists, e.g., intact anti-TNFα antibodies or TNFR-Fc, due to the immunological environment of the cornea.

Applicant's argument is not found convincing because applicant has not provided sound scientific reasoning or objective evidence *why* one of ordinary skill in the art would have considered the immunological environment of the cornea to differentially affect the immunogenicity of an $F(ab')_2$ antibody as compared to larger Fc-binding TNFα antagonists, e.g., intact anti-TNFα antibodies or TNFR-Fc. Put another way, regardless of the immunological environment, why wouldn't one of ordinary skill in the art consider the smaller non-FcR binding $F(ab')_2$ antibody be less immunogenic than the larger Fc-binding TNFα antagonists, e.g., intact anti-TNFα antibodies or TNFR-Fc?

Furthermore, applicant's argument does not appear to take into account that "In the setting of corneal transplantation, the presence of LC [langerhans cells] in the donor cornea has been shown to effect host allosensitazation and graft rejection…***sensitization of the host in corneal grafting requires the participation of host antigen-presenting cells, in a process known as indirect sensitization***…Since in clinical corneal transplantation patients receive central corneal buttons devoid of LC, it is believed that the "indirect" pathway for corneal allograft recognition ***may involve activation of migration of recipient LC from the limbus to the donor corneal tissue where they can acquire foreign antigen***…Two lines of indirect evidence suggest that LC migration is a critical element in host allosensitization. First, the number of infiltrating host LC in the graft bed is predictive of the swiftness with which the host acquires donor-specific delayed type hypersensitivity (Yamada et al.), and the promotion of corneal allograft survival by IL-1 receptor antagonist (IL-Ira) has been correlated with suppression of LC migratory capacity (Dana et al., 1997). Beyond these observations in experimental models of corneal transplantation, ***migration of limbal LC into the cornea has been associated with loss of ocular immune privilege***…and other immunoinflammatory events in the cornea such as development of herpetic keratitis…." See Reza Dana page 3, 2nd paragraph to page 4, 1st paragraph, emphasis added.

Since corneal allograft rejection is pathologically characterized by leukocytic infiltration into the graft stroma one of ordinary skill in the art would consider the immunogenicity of the administered anti-TNFα agent a significant consideration.

Reasonable expectation of success

Applicant further alleges that "…there was no reasonable expectation that the alleged advantages of using F(ab')2 antibody fragments in treating a tumor tissue would succeed in treating corneal transplant rejection. The Examiner must not rely on hindsight, for example, using Applicants' own specification as a blue print, to speculate whether there was a reasonable success of using F(ab')2 antibody fragments to treat corneal transplant rejection."

Applicant's argument is not found convincing because as put forth in the previous Office Action at page 5, 4th paragraph, "One of ordinary skill in the art would have had a reasonable expectation of success in treating corneal allograft rejection via topical administration of a TNFα antagonist, such as an anti-TNF $F(ab')_2$, not only in view of the teachings of Pluenneke but also given the successful treatment of murine corneal allograft rejection via topical administration of a different TNFα antagonist, soluble TNF receptor I (see Reza Dana, in particular, Figures 3 and 6; page 9, 1st paragraph; the paragraph bridging pages 12-13)," and applicant has not convincingly argued why the teachings of Pluenneke, and especially Reza Dana, would not have provided one of ordinary skill in the art with a reasonable expectation that they could successfully treat corneal allograft rejection with an anti-TNF $F(ab')_2$ as of applicant's date of invention.

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

5. New claim 63 is rejected under 35 U.S.C. 103(a) as being unpatentable over John Pluenneke (US 2001/0021380) in view of Fabrizio et al. (EP 0 492 448 A1), Horwitz (WO 92/22324), Adair et al. (EP 0 516 785 B1), Looareesuwan et al. (Am J Trop Med Hyg. 1999 Jul;61(1):26-33, cited herewith) and Reza Dana (WO 00/27421).

Pluenneke teaches a method of treating corneal transplant rejection with anti-TNFα antibody such as the antibodies described in EP 0 492 448 (Fabrizio et al.) and EP 0 516 785 (Adair et al.) (see Pluenneke, in particular, paragraphs [0032] and [0071]). Pluenneke further teaches that TNFα antagonists may be administered via eyedrops (see Pluenneke, in particular, paragraphs [0026]).

Pluenneke differs from the claimed invention in that Pluenneke does not explicitly teach the use of a polyclonal "$F(ab')_2$" anti-TNFα antibody fragment.

However, it has long been known to one of ordinary skill in the art that $F(ab')_2$ antibody fragments, including $F(ab')_2$ anti-TNFα antibody fragments in particular, can effectively neutralize their target antigen, such as TNFα, while at the same time being less immunogenic in a human patient than an intact non-human antibody, easier to grown in microbial cells than an intact antibody, and have better tissue penetration than intact antibodies.

For example, Fabrizio teaches "The term 'antibody' is also meant to include intact molecules as well as fragments thereof, such as F_v, Fab and $F(ab')_2$, which are capable of binding antigen. Fab and $F(ab')_2$ fragments lack the Fc fragment of antibody, clear more rapidly from the circulation and may have less non specific tissue binding than intact antibody. It will be appreciated that F_v, Fab and $F(ab')_2$ and other fragments of the monoclonal antibody of the present invention may be used as well as the intact antibody for the same purposes, e.g. the detection of TNFα and treatment of those disease states in which TNFα has been shown to play a detrimental role." (see Fabrizio, page 5, 1st paragraph and claim 6).

While antigen-binding antibody fragments clear more rapidly from the circulation than do their larger brethren as described by Fabrizio above, it is also common knowledge in the art that due to their smaller size and lack of an Fc region F(ab')2 have better tissue penetrating ability than intact antibodies as taught by Horwitz with respect to heterodimeric $F(ab')_2$ fragments in particular: "The heterodimeric $F(ab')_2$ are preferred over known bispecific antibodies in their properties of a smaller molecular weight and the deletion of the Fc region, which can be advantageous when better tissue penetration and minimization of Fc-receptor cell interactions are desired." (See Horwitz paragraph bridging pages 15-16).

Horwitz further teaches a microbial based expression system for $F(ab')_2$ which enables the expression of antigen-binding antibody fragments such as $F(ab')_2$ directly from bacteria or yeast thereby allowing for the production of these antibody fragments without having the complications of incomplete proteolysis or nicking associated with traditional proteolytic means for making such antigen-binding antibody fragments (see page 5, 1st paragraph).

The teachings of Adair, another patent referenced by Pluenneke for its teaching of anti-TNFα $F(ab')_2$ antibodies suitable for treating, inter alia, corneal allograft rejection, echoes those of Fabrizio and Horwitz concerning the use of $F(ab')_2$ anti-TNFα antibodies to treat TNFα mediated inflammation and the ability to produce $F(ab')_2$ in microbes (see Adair, page 6, 1st paragraph and paragraph bridging pages 6-7).

Given the reference teachings, it would have been obvious to one of ordinary skill in the art, and one of ordinary skill in the art would have been motivated to treat corneal allograft rejection with an $F(ab')_2$ fragment of an anti-TNFα antibody since such fragments have a number of generally useful features such as their ease of production and low immunogenicity (relative to intact non-human antibodies), and TNFα antagonistic activities equivalent to intact antibodies, as well as a specifically useful ability to penetrate tissues which could help in gaining access to the inner eye so as to neutralize TNFα where it is inducing inflammation subsequent to corneal transplantation.

As to using a "polyclonal" $F(ab')_2$ anti-TNFα antibody in the claimed method of treatment, this limitation is taught by the Fabrizio reference cited in Pluenneke for its teachings of anti-TNFα antibodies (see page 2, 10th paragraph). It would have been obvious to one of ordinary skill in the art that polyclonal anti-TNFα antibodies, while less desirable than monoclonal anti-TNFα for in vivo therapeutic use as taught by Fabrizio, can nonetheless be

used to neutralize TNFα. For example, see Looareesuwan page 26 Abstract and Introduction which describes the use of a polyclonal anti-TNFα Fab to treat human disease.

One of ordinary skill in the art would have had a reasonable expectation of success in treating corneal allograft rejection via topical administration of polyclonal anti-TNF $F(ab')_2$ antibody not only in view of the teachings of Pluenneke and Looareesuwan but also given the successful treatment of murine corneal allograft rejection via topical administration of a different TNFα antagonist, soluble TNF receptor I (see Reza Dana, in particular, Figures 3 and 6; page 9, 1st paragraph; the paragraph bridging pages 12-13).

In conclusion, given the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Thus, the instant claims are unpatentable over Pluenneke, Fabrizio, Horwitz, Adair, Looareesuwan and Reza Dana.

6. No claim is allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

   A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ZACHARY SKELDING whose telephone number is (571)272-9033. The examiner can normally be reached on Monday - Friday 8:00 a.m. - 5:00 p.m.

   If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Zachary Skelding
Patent Examiner

/Ram R. Shukla/
Supervisory Patent Examiner, Art Unit 1644